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SERUM-THERAPY OF PLAGUE

IN INDIA ;

A RECORD OF WORK BROUGHT UP TO DATE.

BY

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SPECIAL ASSISTANT HEALTH OFFICER, BOMBAY MUNICIPALITY,
IN CHARGE OF ARTHUR ROAD INFECTIOUS DISEASES
AND MARATHA PLAGUE HOSPITALS.

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The total record comprises 3,195 cases of plague so treated ; the author was personally responsible for 1,515 of the above as they were under his treatment :—

Lustig's	1,163	Cases.
Yersin-Roux'	312	"
Tavel's	28	"
Paltauf's	8	"
Japanese	4	"
Total					1,515	"

Lustig's and Yersin-Roux' serums have had fairly extensive trials ; the results from the latter have been found to be better by nearly 10 per cent. than with the former. The perfection of the serum, and greater confidence in its use, brought about by longer experience as obtainable in the more recent observations are responsible for them. If the earlier cases treated at about the same time as these with Lustig's serum, be however compared, the case mortality is found to be approximately equal.

The author's views on the utility of Lustig's serum as also on the Serum-Therapy of Plague in general, discussing the limitations imposed by the complex nature of the affection, its great and appalling virulence, the late stage at which hospital cases are treated and the wide differences in results between hospital and private patients, having been already placed before the profession in a separate volume* do not need to be reiterated here. Such points of interest connected therewith, as have a bearing on the subject will be brought out in the following pages. The other serums having failed to exhibit any marked efficacy or on account of the observations with them having been limited in number will not require any further consideration. This publication will therefore discuss the recent observations connected with Yersin-Roux serum only.

There exist two schools of thought in the field of plague serum-therapy :—those who are actually engaged at the bed-side in the practical application of the serums, and others who play the role of critics but without any personal acquaintance with the subject. Whilst the former class is almost unanimous in testifying to the beneficial effects of the serums in the bubonic—the most widely prevalent type of plague, especially when non-septicæmic, and has succeeded in practically demonstrating their utility by the results obtained, the latter refuse to acknowledge their conclusions, even when observations conducted on the lines suggested by themselves have

* The Treatment of Plague with Prof. Lustig's Serum. Bombay. 1903.

substantiated the same. They discard all evidence in favour of the serum treatment; whilst they recognise the unfavourable results and accept them as such without thoroughly investigating the cause or causes of such failures—apparent or real. Such an attitude of mind is indeed to be deplored where an issue of great scientific importance, capable of doing immense good, is at stake, but that it does prevail in the world that prides in calling itself scientific, is illustrated by the volume on Serum-Therapy of Plague in India edited by Lieut.-Col. Bannerman,* I.M.S. As the author could not accept the various inferences and conclusions arrived at therein he addressed a representation to the Sanitary Commissioner with the Government of India, under whose auspices it was issued. A reply marked “*Confidential*” was elicited and which therefore is not available for publication. Beyond however pointing out an error in one of his arguments, by way of illustration, as to how mistakes in matters scientific are liable to be made even by the best of observers, but which did not in the least affect the author’s contentions, the reply made no attempt to refute them or to challenge the conclusions he had deduced therefrom. As to why a matter of such scientific importance which had been publicly discussed by the Bombay Corporation should have been treated as *confidential*, I would leave it to the reader to infer.

The following extracts give the principal arguments advanced in the representation in favour of serum treatment.

*Covering Letter to the Sanitary Commissioner
with the Government of India.*

“I have the honour to submit the following representation with regard to the views and conclusions arrived at in volume No. 20 of the Scientific Memoirs re. the Serum-Therapy of Plague of India edited by Lieut.-Colonel W. B. Bannerman, Director of the Plague Research Laboratory, Bombay. Having been personally engaged in the study of the serum treatment of plague for the last eight years and having had exceptional opportunities of observing the clinical effects of the various serums hitherto tested over more than 2,000 plague cases, I would beg leave to state that the subject has been neither fully nor fairly reviewed by the editor, and should his conclusions and those of Haffkine be accepted

* Scientific Memoirs by Officers of the Medical and Sanitary Departments of the Government of India (New Series) No. 20, Serum-Therapy of Plague in India by Lieut.-Col. W. B. Bannerman, I. M. S., M. D., Director, Plague Research Laboratory Bombay, 1905.

without protest, an erroneous impression would be created to the effect that the serum treatment of plague was of no practical value.

Considering the great importance of the subject and the encouragement it has consistently received through liberal grants from the Bombay Municipal Corporation, I have ventred to place this representation before you, in the interests of science, no less than of humanity, and in the hope that you would be pleased to give it your earnest consideration in the light of the arguments advanced therein."

EXTRACTS FROM THE REPRESENTATION.

1. It would be presumed that a publication with the comprehensive title of "Serum-Therapy of Plague in India" would include within its province the records of the principal workers, their original reports, as well as the conclusions arrived at by them from their studies. The editor, however, has considerably restricted its scope by limiting the publication to the work and reports of the Officers of the Plague Research Laboratory and thereby excluding the original work of those who had by far the largest share in the treatment of plague by this method, than all the officers of the laboratory put together.

2. The Memoirs open with a review by the editor of the results obtained in 2,270 cases of plague treated with various anti-plague serums as under:—

With Lustig's Serum	1,551 cases
With Roux-Yersin Serum	535 do.
With Terni's Serum	112 do.
With Brazil's Serum	72 do.

Then follow various reports by the medical officers belonging to the laboratory. Curiously enough, however, the original

reports of the larger number of observations conducted with the Lustig's serum are omitted, presumably on the narrow technical ground that the workers were not officers of the laboratory. Such objections, however, could have been easily met by quoting full abstracts in order to show that there was another aspect of the question as well, and that there existed views and opinions materially differing from those entertained by Haffkine and the editor. This important omission renders the volume incomplete inasmuch as it presents only a one-sided picture and that, too, the least favourable. The complete avoidance of all reference to views opposed to the conclusions formulated therein must create an erroneous impression, that there existed none and that the last word on the subject had been pronounced by the volume. Whilst Haffkine's analysis of the records of our work in one particular series of cases treated with Lustig's serum, that were submitted to him under orders of Government, is almost fully published, not a word is said about our views or contentions. And even the fact that while Haffkine analysed our records by one particular method, peculiarly all his own, there existed another report analysing the same but by a different method and that there was great divergence between the conclusions arrived at is not mentioned. Fairness and justice demanded that a subject fraught with such importance should have been fully and fairly treated, and the obverse as well as the reverse of the picture placed before the reader.

THE ALTERNATE SYSTEM.

3. The interest of the volume and the conclusions arrived at therein centre in the series of observations made with various serums on the "Alternate System"—the system in which every second patient is left untreated to form a control for purposes of comparison. It was assumed that the cases left untreated would be *strictly comparable* with those receiving the serum treatment because they happened to follow in a particular sequence and thus the utility of the serum could be easily demonstrated. When the system was introduced, partly on the suggestion of Haffkine and partly on that of the Indian Plague Commission, on the ground that it had given good results in the serum-therapy of diphtheria, we strongly resisted its adoption, as from clinical experience of the disease and of the character, class and condition of the patients admitted into our hospitals, we honestly believed it to be unsuitable and inapplicable to a disease like plague! We contended that because it was found suitable in diphtheria, there was no reason to conclude that it would be equally suitable in plague, inasmuch as there existed great differences in the nature of the two affections and the conditions of European and Indian hospital practice. We pointed out that there could be no compa-

parison between diphtheria and plague and demonstrated the essential differences between their nature as under:—

	DIPHTHERIA.	PLAGUE.
<i>Class of Patients.</i>	European without racial differences in mortality.	Indian, of various races and nationalities with varying predispositions and mortality rates.
<i>Time of Treatment.</i>	Early common.	Early exceptional; late usual.
<i>Period of greatest Fatality.</i>	10-15 days.	4-6 days.
<i>Normal Mortality rate.</i>	20-30 per cent.	89 per cent (at Bombay). probably higher; 60 per cent. of all deaths in hospitals occur within 48 hours of admission.
<i>Factors Influencing Mortality.</i>	(a) Nil. (b) Nil. (c) Diphtheritic paralysis.	Mortality chiefly influenced by the early and grave cardiovascular paresis, a factor existing in almost every case. Mortality influenced by age, sex, duration of illness, type of plague, location of buboes, &c. Nil.
<i>Blood Infection.</i>	Septicæmia hardly any.	Septicæmia in 60 per cent. of hospital cases.
<i>Toxins.</i>	Toxins, free and soluble.	Toxins, Intra-protoplasmic, requiring disintegration before neutralization and elimination.
<i>Treatment.</i>	Antitoxic.	Antibactericidal and Antitoxic.

4. The attention of the Indian Plague Commission was drawn to the above radical differences between the simpler, longer, and less fatal disease like diphtheria and the complex, short, virulent and fatal infection of plague. Professor Sir A. E. Wright, who took a special interest in the subject, whilst admitting the validity of these arguments contended that in a sufficiently large series of observations there would be such an equal distribution of cases between the two groups as to leave no room for disparity. These anticipations were not realized in a series of 968 cases treated with Lustig's serum. It was also pointed out that there would be unequal distribution of cases as moribund and semi-convalescent patients would have to be included in the two groups, as also the fact that the conditions under which our plague hospitals received patients and where about 60 out of every 100 deaths occurred within 48 hours of admission, would forbid expectations of good results from the application of any serums however potent, by such a system.

5. All the above objections were however overruled. The accumulated experience of clinicians was rejected in favour of the preconceived notions of bacteriologists and it was determined that the method of testing the efficacy of the serums was to be by the "Alternate System." To obtain "controls" in the case

of susceptible animals in the laboratory where all the conditions of experiment are exact and well known ; where the method of infection, the quantity of virus injected and its virulence as well as the quantity of the antitoxin required to neutralize the same are definitely known and under the control of the observer is simple enough. But to obtain a group of "control patients" *strictly comparable* with another group treated with the serum is a practical impossibility in a disease like plague. For, however much age, sex, the type of plague, position of buboes and even the duration of illness—factors influencing the mortality—be made to equalise, the chief determining factor, *viz.*—a corresponding condition of the circulation as shown by the frequency, volume, tension and character of the pulse can under no circumstances be always found in strict and comparable correlation. And yet upon this factor *alone* the prognosis of a plague case depends. Given two patients of the same age, same sex, same type of disease, same position of bubo, the same duration of illness, the same temperature and the same treatment, death or recovery would be ultimately determined solely by the state of the circulation showing the extent to which the cardiovascular paresis has advanced. For, be it remembered, *plague kills at the heart*. That patient in whom it has not far advanced would eventually recover and the other however apparently promising would succumb. Unless, therefore, the condition of the circulatory system is found to be equal or rather approximately so, no two plague cases, however similar in other respects, could be held to be strictly comparable for any purposes of comparison. This cardinal fact so well known to every clinician was entirely overlooked in all the observations conducted on the alternate system.

RESULTS OF THE SERUM-THERAPY OF PLAGUE.

6. The results of the serum treatment have been tabulated by the editor in his summary. The first statement comprises the results of the treatment as carried out on the alternate system "those in which the conditions of trial were reasonably accurate and where a series of *control patients strictly comparable* for one reason or another with those receiving the serum treatment." The second statement included those cases in which "though the records of the serum treated cases may be accurate yet the control patients where such are reported were not in all respects comparable for one reason or another with those receiving the serum treatment." The observations comprised in the latter table have been wholly ignored, the editor refraining from offering any comments thereon ! To the clinician, however, they were of great significance inasmuch as they were undertaken, so far as Lustig's serum was concerned, with which 946 patients were treated, not with the view of demonstrating its statistical value as for determining its clinical effects. No so-called control cases were therefore included for comparison, and if comparison had

to be subsequently instituted, it was not so much for its statistical value as for showing what effect the serum had in lowering the mortality rate in those cases that were *really fit for serum treatment* and not beyond all hope. On this basis the results obtained were such as to demand careful consideration as they indicated a distinct lowering of mortality. And so also in the 130 cases treated in private practice by 10 medical gentlemen, the rate of mortality was as low as 44.61 per cent. These results have been similarly ignored. No attempt has been made to explain how it was that there was such a great reduction in the mortality. The editor contents himself simply by remarking "No contrasting cases." But there could not be any, as a matter of course, among private patients! The above observations with Lustig's serum left no doubt on the minds of those who observed them from day to day that it exerted a distinctly beneficial influence on the course of the disease, ameliorated the symptoms and saved more lives. The details in connection with this I have fully described in my book on the treatment of Plague with Prof. Lustig's serum, a copy of which I had the pleasure to forward to the Sanitary Commissioner some time back.

7. If we now turn to the first table it gives food for much reflection. The observations with the alternate system have been summarized by the editor from a most ingenious, elaborate and strictly arithmetical analysis—the invention of Haffkine—in which each case has to be analysed into 8 tabulations and docketed into something like eight to ten times as many sub-divisions. It is a most intricate system where the thermometrical readings, the frequency of the pulse and the number of respirations—all numbers—play the most important role and where the results of such an inexact science as medicine have been made to justify themselves by the test of the exact science of numbers. Such a system may be a good exercise at arithmetic, but it certainly is not and cannot be called *medicine*. And so far as we are aware it has not been adopted in analysing results obtained by medical or serum treatment in the case of any other disease. Too much importance—far more than what is actually deserved as any clinician can testify—has been attached to the range of temperature, to the frequency of the pulse and to the number of respirations. A high temperature in plague may be and generally is an index of the gravity of the case, but a low temperature does not mean the converse. In every case of plague there is a remission of temperature on the third day and although the previous reading may be as high as 105°, the lower reading of 101° or even so low as 98° or 97° does not imply that the patient was not in a serious state if he happened to be admitted at the time. It is only by thorough familiarity with and constant attendance on plague patients that any valid analysis of the range of temperature can be of use, as there are so many causes slight as well as grave, that send up the temperature in a plague patient both during the

acute as well as the convalescent stage. The serum, it must also be remembered, is not an antipyretic drug like antipyrin or phenacetin. It has no direct influence on thermogenesis or thermolysis. If it does contribute to the lowering of the temperature, it is by its indirect action on the plague virus. To expect therefore a lowering of temperature after each injection, just as after the administration of an antipyretic drug, and to analyse the records of temperature without looking into the results *as a whole* cannot be considered strictly accurate. The injection of serum on or after the third day of illness does not generally shorten the normal course of the disease as well as of the fever which is about 10 days in all uncomplicated cases. Should it be, however, injected within the first 12 or 24 hours or even within 48 hours the course is considerably curtailed, in the former instance to 4—5 days and in the latter 6 to 8 days, and the fever leaves the patient. Thereafter it is possible that the temperature is controlled but its period is not shortened. The mere determination therefore of the day on which the temperature of a patient reached to normal in a particular case is of small value without detailed information of the other circumstances of the case. A foot rule and a thermometer are but broken reeds to rely upon, in the prognosis of a plague case and the physician who depends upon them would soon come to grief. And so also with regard to the frequency of the pulse to which so much importance has been attached by Haffkine. It is *not* the frequency that is of so much value as the volume, tension, compressibility and other characters of the pulse which are to be *felt* by the *tactus eruditus*, but which cannot possibly be expressed by figures or numerals on the clinical records, and yet we have been asked to take these numerals, seriously and to consider the results built upon them! Great frequency alone might indicate gravity, but moderate or low frequency does not mean the reverse in the majority of cases. Similarly with regard to the frequency of respirations which is such an uncertain factor. Respirations are increased in frequency by trivial or grave causes, *e.g.*, attempt at sitting up, removal to hospital, delirium or any slight exertion and the mere counting of respirations is no criterion of the gravity of a case. On the other hand, when there exists such a grave complication as plague pneumonia simple or complicating bubonic cases, the number of respirations may not be higher than what would correspond to the range of temperature and there would be no indication of the gravity of the case. The whole system of analysis, except in one or two instances, is mere reduction to figures with results that appear paradoxical to Haffkine, who has woefully failed to realize that the causes of the apparent paradoxes lay *not with the serums but with his system* of treatment and method of analysis. Thus therefore between an unscientific and inapplicable system on the one hand and an ingenious reduction to figures on the other, the serums have had no fair chance to exhibit their beneficial effects.

ROUX-YERSIN SERUM.

8. The case for the serums however is fortunately not so hopeless as Haffkine and the editor would have us believe and there are grains of comfort to be gleaned even from this chaff of numbers. If we now consider the observations with the Roux-Yersin serum, five series comprising 226 cases have been tabulated by the editor. He evidently does not know of the existence of another series of 35 cases treated at the Modikhana Hospital by Dr. Mayr between December 1901 and February 1902. These 226 serum cases had a mortality rate of 74·33, whereas the 231 control cases showed it 70·56, the difference in favour of the control cases being 3·77 per cent. *

* * * * * The editor "reluctantly concludes that the serum treatment as judged by these figures did not affect the case mortality in the slightest degree." *

* * * * * The above results have been accepted as facts, but no real attempt, in spite of all show of fairness and impartiality, appears to have been made to trace their cause. And yet it would not have required great labour to demonstrate that there was another side to the question. Having no personal experience with the first 3 series of observations with the Roux-Yersin serum in the tabulation we shall consider only the last two adding Dr. Mayr's observations above referred to:—

	Serum cases.				Control cases.			
	No.	Deaths.	Recoveries.	Case mortality per cent.	No.	Deaths.	Recoveries.	Case mortality per cent.
Roux-Yersin serum by Dr. Mayr 1901-1902, Modikhana Hospital. ...	35	24	11	68·59	35	29	6	82·85
Roux-Yersin serum by Dr. Mayr 1902,* Maratha Hospital ...	31	29	2	93·54	31	29	2	93·54
Roux-Yersin serum by Dr. West 1904, Maratha Hospital ...	68	45	23	66·17	68	41	27	60·29
	134	98	36	73·13	134	99	35	73·88

* This series was not strictly alternate as the first patient was treated with Roux-Yersin serum, the second with Lustig's and the third was left as control and so on.

From the above tabulation we too must reluctantly conclude that the serum treatment had no influence in reducing the mortality ! If however we look a little beneath the surface we at once realize where the difficulty lay. It did not lie with the ineffectual serum, but with the faulty alternato system inasmuch as instead of an equal distribution of favourable and unfavourable cases—of cases strictly comparable—as so fondly anticipated, we find that the serum cases were placed at a distinct disadvantage by the inclusion of 52 septicæmic cases that proved fatal, against only 36 such cases in the control group* who also succumbed. If we eliminate these cases an altogether different result is brought to view:—

	Serum cases.				Control cases.			
	No.	Deaths.	Recoveries.	Case mortality per cent.	No.	Deaths.	Recoveries.	Case mortality percent.
Roux-Yersin serum by Dr. Mayr 1901-1902, Modikhana Hospital.	17	6	11	35.29	20	14	6	70.00
Roux-Yersin serum by Dr. Mayr 1902, Maratha Hospital.	16	14	2	87.50	18	16	2	88.88
Roux-Yersin serum by Dr. West, 1904, Maratha Hospital.	49	26	23	53.06	60	33	27	55.00
Total ...	82	46	36	56.01	98	63	35	64.28

DIFFERENCE IN FAVOUR OF SERUM CASES 8.11 PER CENT.

If we compare the two statements we see at a glance how and under what circumstances the Roux-Yersin serum actually saved more lives. They further demonstrate the fact that although the patients were treated alternately *the control cases were not strictly comparable with the serum cases*, and that there was unequal distribution of septicæmic cases, the serum group having 52 against 36 in the control group. They also indicate that not one of the 88 septicæmic cases recovered whether treated with or without serum. These results further corroborate the conclusion I arrive at

* The septicæmic cases were thus distributed :—

	Serum cases.	Control cases.
Dr. Mayr's Modikhana Hospital.	18	15
Do. Maratha Hospital.	15	13
Dr. West's Maratha Hospital.	19	8
	52	36

at with regard to the utility of the serum treatment in my book above referred to *viz*:—

- “ 2. That the serum—Lustig’s or Roux-Yersin’s—is capable of considerably reducing the case mortality of plague in the non-septicæmic cases, but that in the septicæmic, (when plague bacilli are found in blood by culture) both are equally of no avail, they cannot avert death, all that they do is to prolong life.”*

There can be therefore no hesitation in concluding that although the Roux-Yersin did not show a higher percentage of recoveries when tested on the alternate system on account of the unequal distribution of septicæmic cases in the two groups, on eliminating the latter and comparing the non-septicæmic cases it showed a distinct and appreciable gain on the serum side and that the serum was after all not so devoid of good influence in reducing the mortality. A difference of over 8 per cent in mortality means the raising of the ratio of recovery by about 25 per cent., that is, from 36 per cent. to 44 per cent.

LUSTIG’S SERUM.

9. Of the four series of cases included in the table the, largest series of 484 cases will alone engage our consideration. The 66 cases treated at the Modikhana Hospital were personally investigated at the time by Colonel J. W. S., Wilkins, I. M. S. who declared “the results to be valueless” and “the observations for all intents and purposes useless” as they were carried on without any system, although they were supposed to have been carried out on the alternate system. The rather belated explanation of the irregularities in a private communication to the editor, more than four years after the event, does not therefore affect the above conclusion. And similarly Costello† interfered with the sequence of cases at Poona. The most essential requirement has been entirely overlooked, *viz.*, that once a particular system is adopted, it should be rigorously adhered to, as any deviation therefrom or arbitrary interference with it vitiates the results. No circumstances ought to be allowed to interfere with the natural sequence of cases, and had that been done, Costello’s cases as re-arranged by Dr. Mayr, instead of showing 6 recoveries on the serum side and 8 on the control, would have shown 10 recoveries on the serum side and 6 on the control even supposing that the serum was inefficacious. Whatever the causes that led to the exclusion of five cases the fact remains that by their exclusion the natural sequence of alternation was interfered with and an element of doubt introduced which ought to have been most rigidly kept away. The editor has not a word to say about this. The failure of the serum is to him an accepted fact!

* *Vide* the Treatment of Plague with Prof. Lustig’s Serum, by the Author ; pages 90-91. † Also page 122.

10. And now we turn to the largest series of 484 cases treated at the Arthur Road Hospital. The cases were taken in strict alternation *without a single exclusion* and when compared with an equal number of control cases, showed a difference of 11·5 per cent. in favour of the serum cases. And here comes a contrast. The Indian Plague Commission who were partly responsible for the imposition of the alternate system in the course of reviewing these results in their report say :—

“ We have here at last a result obtained by a method which satisfies the demand formulated in a previous section. The diminution of plague mortality by 11·5 per cent in such an extensive series of cases treated with the serum seems to us, assuming as we presume we may do the correctness of the records, conclusive as to benefit having been derived from the administration of the serum.”

The Indian Plague Commission having been partly instrumental in imposing upon us the system, whether applicable or inapplicable, accepted the results in good faith and without any demur. As regards their reservation about the correctness of the records such an overcautious and circumspect critic as Haffkine vouches for the same as well as also for the fact that all the cases were diagnosed by competent medical men. The testimony of the Indian Plague Commission is therefore conclusive as to the benefit derived from the serum treatment. That is not however sufficient for Haffkine. He does not accept the facts as they are, but straightaway proceeds to ascertain by the aid of his ingenious mathematical system of tabulation “whether the 484 control patients were from the first comparable in their main features with the 484 serum cases and whether the latter would have had more deaths if the serum had been omitted. There are some indications that this may not have been entirely the case.” Which means in plain words the condemnation of the system which he himself was partly privy to imposing upon us and which he considered the best for bringing out the results of the serum treatment ! If one group of cases happened to include more favourable cases than the other on account of unequal distribution there could have been *no strictly comparable cases*. And yet, though Haffkine is constrained to admit this, the editor assumes they were strictly comparable !

11. As regards the preponderance of deaths in the control cases Haffkine says “that it is impossible to maintain that the uneven distribution of cases which in most instances was quite unavoidable accounts for the same, for in certain other subdivisions showing a lessened but still high mortality there was a considerable though less preponderance of serum cases.” In other words, though in some instances the serum group did not at all seem to be favoured in any way by milder cases it showed

lower mortality. In spite of this admission Haffkine will not give credit where it is due and withholds what any fair-minded observer would have readily given under the circumstances, *viz.*, to the application of the serum. "But it is impossible also to say with certainty" he adds "how many of the excess survivals, if any, are due to the serum." And Haffkine does not realize that what he calls his "corrective",—that in every instance in which a choice has to be made between two patients admitted to hospital at the same time, the more severe case be taken for serum treatment and the milder one for the purposes of "control observations"—is as much an arbitrary interference as any deliberate selection, as it changes the sequence of cases and also introduces an element of selection that is obviously unfair to the serum treatment. If the mortality is influenced favourably in these circumstances, says he "a proof is obtained *a fortiori* of the beneficial action of the treatment applied." In other words, it means that every time two patients happen to go to the hospital simultaneously, they are not to be taken for observation in the sequence in which they may be registered by the admitting clerk, but that the more severe of the two should be invariably assigned to the serum group and if such cases recover, then only would it be proof positive of the beneficial effect of the serum! "This postulate has not been complied with in the case under consideration" says Haffkine. Of course not. And for the simple reason that our instructions were to treat the cases alternately without any interference in their sequence and Haffkine's "corrective," if it be called one, was not then even known or brought to our notice. We took extraordinary pains to adhere most rigidly to the system imposed and we are now told that we did not add a "corrective" to it. To impose a system first and then to invent a "corrective" to hide its manifest imperfections seems rather incongruous. It is a tacit admission of its unsuitability. It is painful to note that at every step and in spite of ample evidence, Haffkine fails to realize that the system of which he claims the partial paternity is by no means the perfect system he imagined it to be and that our contentions of its inapplicability to plague have been proved to be valid through his own handiwork. The paradoxical results that he talks of are not paradoxes to the clinician familiar with the bedside of the patient and the many vicissitudes through which a plague patient has to pass before he can be said to be on the high road to recovery. No useful purpose would be served by their detailed examination but a comparison between the simple and sensible analysis that we made and that of Haffkine's would explain these alleged paradoxes which appear so inscrutable to him. These pseudo-paradoxical results seem to suggest to him "that in the facts observed there were apart from the serum injections *other factors* which influenced the course of the disease and the recovery or death of the patients very powerfully." To us who see no paradoxes

and no "other factors", the results are a complete and irrefutable proof of the benefit of the serum treatment as tested even by the alternate system to which Haffkine and the Indian Plague Commission had both nailed their colours. And while the latter abide by their system, Haffkine comes forth, rather too late, to condemn it in order to belittle the results which perhaps unexpectedly for him happened to be favourable to the serum treatment. Whilst Haffkine is not prepared to apportion how much of the better results could be assigned to the serum and how much to "other factors"—what factors he does not mention—the editor reluctantly arrives at the conclusion "That judged by these figures (Haffkine's) alone there is no certain evidence that the serum is efficient!" And yet it is on the score of the cost per patient treated that Haffkine says "that the results are not favourable to a general adoption of the treatment" and not because the serum was inefficient or entirely useless.*!

12. The editor in his summary recapitulates the beneficial effects of the serum observed clinically and admits "that in such a virulent disease as plague is in India, these are no small gains, especially as 60 per cent. of the bubonic cases are on admission to hospital septicæmic." And yet he does not recognise the fact, that whilst the serums have hitherto proved of very little value in the septicæmic cases, they have shown a marked reduction of mortality in the non-septicæmic, as the tables he summaries indicate, when tested by even such a system as the alternate. He mentions that Roux—but ourselves more than he—have repeatedly urged that "it is quite out of the question to expect to get any results with cases far advanced in the disease and that therefore the alternate method hitherto tried in Indian Hospitals is not one to bring out the true value of the serum treatment." Just so. It would not have cost the editor much time to prove or disprove the above assertions from the data at his disposal. And had he done so, he could not but have been compelled to admit that our estimate of the alternate method was correct and was fully borne out by the very analysis and reports he edited. He contents himself however with a suggestion, which, he does not appear to be aware, had been actually put into practice:—"But perhaps it would be possible" says he "to get an experienced clinician to select such cases as he deemed suitable for serum treatment, and to admit them to a separate ward where they would be submitted to the alternate method of treatment by an independent observer." It seems that any experienced clinician who would essay to select such

* With regard to the cases treated with Terni's serum on the alternate system in the absence of any details about the distribution of non-septicæmic and septicæmic cases, it is not possible to judge of its effects. In the series of cases treated with Brazil's serum there were 17 septicæmic cases in the serum group and 20 in the control. The difference in favour of the serum cases, after excluding these from both the groups, was 2.65 per cent. The number of cases treated was however too limited for a positive opinion.

cases must depend solely for such selection upon the state of the circulation of the patient as indicated by the pulse, and that all other factors, however favourable they may appear, must be counted of subordinate or small value. His selection must be, by this *the only method*—and not from the low range of temperature, nor from the lesser number of pulsations, nor from the frequency of respiration, nor from the type of plague, nor from the position of bubo, &c. Such a method has been tried and with what results we shall see further.

13. The above review of the conclusions of our critics implies that the serums have not been fortunate in them and that they have failed to take a fair and unbiassed view of the subject, and to realise the imperfections of a system totally unsuited and inapplicable to a disease like plague, and rather than honestly admit its imperfections have attributed the unsatisfactory results to the inefficacy of the serums. It cannot be contended by them that they have discharged their duties impartially, inasmuch as they do not appear to have taken any pains to investigate whether the serums are really so devoid of beneficial effects as to be inefficacious in all cases and under all circumstances. They have not acknowledged the facts disclosed by their own analysis, and have not had the fairness to admit, as they ought to have, that the serums have considerable effect in reducing the mortality of cases that are not septicæmic. They have ignored the results of cases treated by other and more rational methods and in private practice and have not been able to challenge by a single observation or argument the recital of almost marvellous and instantaneous beneficial effects exerted by the serums on cases treated on the first day of the disease. In fact, whilst they have willingly, nay rather too eagerly, accepted all evidence against the serums, they have not even half-heartedly acknowledged that there was other evidence in its favour. The whole subject has been looked into by these critics from the narrow standpoint of the laboratory and the bacteriologists (one of them not even a medical man) have drawn their conclusions, not from the evidence of living patients, but from the dead and soulless sheaves of papers, but imperfectly and hurriedly inscribed by the over-worked nurses in the storm and stress of the plague epidemics. The combined experience and observations of the clinician, long familiar with the disease in all its phases have been set at naught, and the word of the bacterio-

logist has had full sway. And the result—a serious blow to the progress of the serum-therapy of plague.

* * * * *

Then follow the results of serum treatment during 1905.

* * * * *

Such then are the data gleaned from the continuous study of various serums during the last eight years. That the results have not been brilliant or more encouraging has been due to the complex nature of the disease, its great virulence, its rapid course and the unfavourable conditions of work in the East, as compared with altogether better conditions obtaining in the West when dealing with a milder disease like diphtheria. We may now sum up the present position of the serum therapy of plague:—

1. That Lustig's and Roux-Yersin's serums are both equally efficacious in ameliorating symptoms and prolonging and saving more lives in plague.*

2. That both the serums have shown considerable reduction in mortality in cases that are not septicæmic at the time of treatment, but that in septicæmic cases they have only ameliorated symptoms and prolonged life without ensuring more recoveries.

3. That with the largely extended use of the intravenous method of treatment, it is probable that greater beneficial effects would be observed even in septicæmic cases.

4. That the principal reason why more encouraging results have not been hitherto obtained in hospital practice has been the adoption of a faulty and unscientific system, totally unsuited to the nature of the disease and inapplicable to the conditions of hospital practice in India. The high authority of Prof. C. J. Martin may be cited in support of this.

5. That when tested on a large number of cases suitable for serum treatment in hospital practice, the reduction of mortality has been very marked, and if adopted for all patients suitable for such treatment a reduction of 20 to 25 per cent. on the total mortality can be obtained.

* Haffkine does not believe that amelioration in symptoms need necessarily tend to an improved mortality rate and quotes in support the instance of cholera where injection of water has a most striking effect 'but the effect on the mortality is so absolutely negative that the injections have been abandoned in practice' Haffkine however forgets that the injection of water in cholera is but a symptomatic treatment—the replenishing of the lost fluid to the system and that the striking improvement is due to improved circulation and not to any specific effect of the water on the cholera virus or toxins. On the other hand, the amelioration of symptoms in plague is due to a distinct specific effect as shown by the hardening of buboes, lesser tenderness and pain and cessation of further extension, general improvement and more recoveries. The injections of water or saline fluids have not been abandoned in the treatment of cholera as Haffkine supposes: their utility has been established beyond doubt and they still form an integral part in the treatment of cholera where adequate facilities exist i. e., at the Arthur Road Infectious Diseases Hospital at Bombay and elsewhere.

6. That the beneficial effects of the serum treatment can be best observed in patients treated within 24 to 48 hours of illness. The whole aspect of plague becomes so greatly altered as to rob plague of its terrors.

7. That if used early, a much smaller quantity of serum is required to effect a cure; even massive doses are ineffectual at a late stage.

8. That in a rapidly progressive disease like plague that kills within four to six days, early treatment is absolutely essential. The delay of a few hours means all the difference between life and death.

9. That the serums have given much better results in private practice for the above reason.

10. That it is desirable to extend largely the use of the serum treatment and that if people will not resort to protective measures, it is incumbent on Government to make every effort to save the population from the ravages of plague by placing the serum treatment within the reach of the poor.

11. That in the opinion of Sir Thomas R. Fraser, Col. T. S. Weir, I. M. S., Col. J. W. S. Wilkins, I. M. S., Major W. E. Jennings, I. M. S., Dr. J. A. Turner, Prof. Dr. Max Schottelius, Prof. Dr. Martin Hahn, Prof. Dr. Dürk and the Indian Plague Commission who have had opportunities of personally observing the effects of the serum treatment as conducted at the Arthur Road and Maratha and other hospitals, the serums have been beneficial and Sir Thomas Fraser considers the results encouraging and justifying the hope that "with sera of greater bactericidal and antitoxic power than those hitherto prepared, more definite therapeutic benefit will be observed."

THE TREATMENT OF PLAGUE WITH YERSIN-ROUX SERUM IN INDIA.

PREVIOUS OBSERVATIONS IN INDIA, 1897.

Yersin, Simond, Mason, the German Plague Commission* and others made a series of observations with the Yersin-Roux Serum in 1897. They treated 309 patients at Bombay, Cutch-Mandvi, Karad and Karachi during the first epidemic of plague, when the full virulence of the disease had not yet declared itself. The results indicated that out of the above number, 166 patients died and 143 recovered, giving a mortality rate of 53·7 per cent. They found that the mortality rate could be considerably lowered if the patients could be treated on the first day of illness. In 39 patients treated on the first day, they had a mortality rate of only 33·3 per cent., that is about 20 per cent. lower than their average. The extremely favourable influence of the serum under such circumstances has been fully corroborated by other observers also.

OBSERVATIONS AT BOMBAY.

OBSERVATIONS AT THE PLAGUE HOSPITALS AT BOMBAY, 1901-03.

During the four subsequent epidemics, the Yersin-Serum—now improved and modified by Professor Roux of the Institute Pasteur of Paris—scarcely received any attention on account of the extended use of Lustig's serum, locally prepared. A few isolated observations were conducted by Dr. Alfons Mayr and myself at the Arthur Road, Modikhana and Maratha Hospitals during 1901-03, numbering in all 77 cases, of whom 58 died and 19 recovered, giving a mortality rate of 75·3 per cent. ; 66 of the above number were treated on the alternate system, and the serum cases exhibited a difference of 7·4 per cent. in their favour as compared with a similar number of cases treated by ordinary methods:—

	No.	Died.	Recovered.	Mortality per cent.
Control Cases	66	58	8	87·7
Serum Cases	66	53	13	80·3
Difference in favour of Serum Cases				7·4

* Report of the Indian Plague Commission, 1902, and Lieut.-Col. Bannerman's Memoirs.

OBSERVATIONS AT THE MARATHA HOSPITAL DURING 1904.

The next series of observations was conducted at the Maratha Hospital during the epidemic of 1904 by Dr. West on behalf of the late Director-in-Chief of the Plague Research Laboratory, under my general supervision. The alternate system was adopted, and 80 patients were treated with the following results :—

	No.	Died.	Recovered.	Mortality rate per cent.
Control Cases	80	50	30	62.5
Serum Cases	80	55	25	68.7
Difference in favour of the Control cases				6.2

The serum group not only showed no advantage over the control, but it had a higher mortality rate by 6.2 per cent. These results have been already discussed in the preceding pages.

OBSERVATIONS AT THE MARATHA HOSPITAL
DURING 1905 AND 1906.

Further observations were made at the above hospital during 1905 and 1906. Instead of wasting the serum on patients whom we knew from past experience to be not amenable to *any* treatment after a certain stage in the disease had been reached, *i. e.*, those actually in the moribund condition, or exhibiting symptoms of grave cardio-vascular paresis, and consequent impending heart-failure, it was determined to apply it to such cases only *in the acute stage*, whose circulatory system had not been so gravely affected and who had a fair, but by no means always, a favourable pulse. All semi-convalescent and convalescent patients were also excluded from the serum treatment for obvious reasons. In order to allow of comparison between the cases treated with and without serum, the use of the serum was suspended during certain intervals, and as the full virulence of the disease lasted during March, April and May in 1905 it was not difficult to secure a sufficient number of comparative observations.

FOUR SERIES OF OBSERVATIONS.

The observations were thus divided into 4 series :—

First Series :—The first series was commenced on 1st March 1905 and lasted till 19th idem. It comprised 102 patients; 89 patients were rejected as unfit for the treatment in accordance with the plan above sketched out. From the 19th to 31st March the serum treatment was suspended for purposes of comparison.

Second Series :—The second series lasted from 1st to 10th April and comprised 53 cases ; 64 cases were rejected as unfit for serum treatment. From the 10th to 20th April, the serum was again suspended for comparison.

Third Series :—The third series comprising 51 cases was commenced on 21st April and lasted till 4th May ; 46 cases were rejected as unfit for serum treatment. It was resumed in 1906 (May-August) and included 30 cases ; 30 cases were taken as controls and 80 cases were rejected ; 20 because they were convalescent or semi-convalescent and 60 as unfit for serum treatment.

Fourth Series :—The fourth series includes 26 patients, treated during January and the latter end of May, and some in June, July and January to May 1906 ; several patients provided the serum at their own cost.

THE SYSTEM OF SERUM TREATMENT.

(a) In the first series, each patient received 2 subcutaneous injections of serum per day, one morning and evening. The serum was injected as close to the proximity of the buboes as possible. The maximum quantity injected per day varied from 150 to 200 c. c.

(b) In the second series, only one injection was given daily in the morning, the maximum quantity injected varied from 50 to 100 c. c.

(c) Whilst the above observations were in progress Prof. C. J. Martin of the Plague Research Commission visited the Maratha hospital, and discussed with me the various systems of treatment. His estimate of the value of the alternate system, as hitherto applied was in accord with what I have said above, and whilst approving of the method already adopted in the first and second series, he proposed that in order to arrive at a fixed numerical demonstration of the value of the serum treatment, some system of simultaneous comparative observations should be instituted. He suggested, that after the rejection of the unfit, as in the first and second series, every alternate case should be treated with the serum, so that those left untreated would be the controls for purposes of comparison. It was this system of what may be called "Rational Alternation," that was adopted in the third series. It comprised 162 cases fit for treatment, 81 of whom were treated with the serum, and 81 left as controls. 126 cases were rejected as unfit for serum treatment. Only one injection of serum was given every morning, and the daily average varied from 50 to 100 c. c.

(d) In the fourth series there was no elimination of the unfit, as most of the patients supplied their own serum and had to be injected. Two injections per day were given as in the first series. It comprised 26 patients only.

THE RESULTS OF TREATMENT.

The following statement shows the results of the serum treatment in the four series:—

	No.	Died.	Recovered.	Mortality per cent.
First Series... ..	102	61	41	59.8
Second „	53	31	22	58.4
Third	81	51	30	62.9
Fourth „	26	15	11	57.6
Total.....	262	158	104	60.3

The results of the third series with the controls may be thus expressed :—

	No.	Died.	Recovered.	Mortality per cent.
Control Cases	81	62	19	76.5
Serum Cases	81	51	30	62.9
Difference in favour of the Serum Cases				13.6

What value the above results represent can be determined by analysing the same in three different directions :—

Firstly.—By comparing the results of the cases treated with and without the serum.

Secondly.—By comparing the third series of the serum and control cases.

Thirdly.—By adding together the serum and rejected cases and comparing their mortality rate with that of the non-serum cases, in order to find out whether there was any, and if so, what influence on the reduction of mortality rate *on the whole* in the former group.

(a) Before entering into the details of comparison, it would be advantageous to note the virulence of the epidemic (1905) in January and February, before it reached its fastigium, which was more prolonged than usual and so far as clinical observations went, extended right up to the end of May. During these two

months 333 acute cases of plague were admitted at the Maratha hospital and the results of ordinary drug treatment were asunder :—

1905.	No.	Died.	Recovered.	Mortality per cent.
January	112	86	26	76·8
February	221	176	45	79·6
Total ...	333	262	71	78·6

The mortality rate during February was about 3 per cent. higher than in January, and as is usual in all epidemics the tendency is to go higher still as the epidemic advances. That it actually occurred is shown by the following statement of non-serum cases, during the intervals when the use of serum was suspended :—

1905.	No.	Died.	Recovered.	Mortality per cent.
March 19th-31st	108	85	23	78·7
April 10th-21st	131	116	15	88·5
May 5th-31st	167	137	30	82·0
Total ...	406	338	68	83·2

It is evident from the above that the three periods during which the serum treatment was applied (1st to 19th March ; 1st to 10th April and 21st April to 5th May) coincided with the period of the maximum virulence of the epidemic, and that whilst the mortality rate in the non-serum cases was 83·2 per cent. it was 62·1 per cent. in the serum group. There was an advantage of over 21 per cent. in favour of the serum cases. On the other hand, it would be argued that the above comparison was not fair, inasmuch as whilst the non-serum group comprised *all* the acute cases, there was considerable elimination of moribund and semi-moribund acute cases in the serum group on account of the system of rejection adopted, and hence the method of comparison was to that extent favourable to the serum cases. That is a perfectly valid objection which will be discussed further on.

(b) The second method of comparison between the serum and control cases in the third series, indicates that in 81 cases treated on either side, the serum cases showed an advantage of over 13 per cent. in their favour. This may be taken to be the expression of the numerical demonstration of the value of the serum treatment in *hospital practice*.

(c) The third method of comparison fully meets the objection raised in the above para, and it will be interesting to note whether the morality was reduced *on the whole*, if the serum, control, and rejected cases, were amalgamated and compared with the cases treated without the serum as under:—

1905 and 1906. (a) Serum (b) Control and (c) Rejected cases.				1905 * Cases treated without Serum.			
No.	Died.	Recovered.	Mortality per cent.	No.	Died.	Recovered	Mortality per cent.
(a) 262	158	104	60.3				
(b) 81	62	19	76.5	406	338	68	83.2
(c) 279	249	30	89.2				
622	469	153	75.4	406	338	68	83.2

Here again we find that in spite of combining the serum group with the control and rejected cases, the results are still favourable to serum treatment. Although only 262 patients were treated with the serum in a total of 622, the mortality rate on the whole was lower by 8 per cent. than in 406 cases treated without the serum. It may be noted that out of 279 patients rejected as unfit for serum treatment, only 30 recovered under the ordinary drug treatment, they were mostly convalescent or semi-convalescent.

On the whole therefore there can be no doubt that there was distinct gain under the serum treatment, and that more lives were saved than under the ordinary treatment.

What influence the nature of the epidemics had on the results of the serum treatment is a question of importance and so also is another *vis*:—Whether the system of treatment adopted favoured or acted adversely to the results. That the character of the last epidemic did not in any way favourably influence the results of the serum treatment is indicated by the comparative tables of mortality rates given in a former para.

Secondly, if the graver manifestations and complications of plague in the serum and non-serum groups be compared the conclusion we arrive at is, that in spite of the system of rejection adopted, the serum patients were in no way favoured, as they actually showed a greater preponderance of such complications. At the same time it should be noted that the serum group showed

* As there was no analogous series of cases treated without serum during the epidemic of 1906, the figures for 1905 only are here given. So far as the virulence of the epidemic of 1906 was concerned, it was practically the same, as that of 1905, the average mortality rate being 89 per cent in both.

proportionately more recoveries from the same than the non-serum group :—

Complications.	262 Serum cases.			766 Control, Rejected and non-Serum Cases.		
	No.	Percent- age to total cases.	Recovered.	No.	Percent- age to total cases.	Recovered.
Secondary Pneumonia	20	7.6	6	28	3.6	1
Coffee-ground vomit- ing.	10	3.8	1	24	3.1
Hæmatomesis ...	1	0.5	5	0.7
Hæmaturia	11	4.1	7		1.5	4
Marasmus	27	10.3	2	26	3.9	1
Meningitis	6	2.2	...	8	1.0
Tympanites (grave) ...	13	4.9	7	2	0.3

THE SERUM TREATMENT IN PRIVATE PRACTICE AT BOMBAY.

Drs. B. Pais, M. A. deHeredia, Alfons Mayr and myself have altogether treated 209 cases in private practice with the following results:—

Observers.	No.	Died.	Recovered.	Case Mor- tality per cent.
Dr. B. Pais	122	50	72	40.9
Dr. M. A. de Heredia ...	48	16	32	33.3
The Author	33	13	20	39.3
Dr. Alfons Mayr.	6	3	3	50.0
Total	209	82	127	39.2

Remarks:—Details of only 107 of the above cases show that they included 17 fatal septicæmic cases; one patient had pneumonic plague; 2 were pregnant—both fatal—one of them being a girl aged about 18, in the fourth month of her third pregnancy. One case, fatal, was over 80 years. In two fatal cases, the

serum injections were prematurely stopped. Two cases were too far advanced for serum treatment, but had to be treated at the earnest solicitations of friends ; both proved fatal. In three fatal septicæmic cases, life was prolonged for 12, 15, and 30 days, the quantity of serum used being 1280, 1520, and 1900 c. c. respectively. In one of them plague bacilli and streptococci were found in the blood on the twentieth day of illness, after 1500 c. c. had been injected. In one fatal case, the temperature rose to 108° after reaching to normal after the first injection of serum, and remaining so for eight hours ; subsequent injections had no influence on the course of the disease.

Among the patients who recovered, one was a case of mixed infection—plague and measles—the latter supervening on the third day of illness, although slight coryza and watering of the eyes *were* present from the first day of fever, together with femoral and inguinal buboes. One Chinaman, who recovered, had 1220 c. c. of the serum in 19 injections. He had a succession of buboes, and after each fresh injection they disappeared from one part to appear at another. A Parsee patient had plague and pyæmic infection with suppuration of both the tunica vaginalis and cold abscesses ; pyæmia developed after the plague symptoms had been well controlled by the serum : anti-streptococcus serum was used and he made a tardy recovery. The buboes became absorbed in 59 cases, among 95 recoveries, that is in 62 per cent. of patients who recovered ; their convalescence was therefore very rapid.

The above details illustrate the limitations and difficulties encountered in the use of serum in private practice. The conditions are not uniformly favourable, and although at first sight the better results may be ascribed to them, there can be scarcely any doubt that they are due to the serum treatment.

The results are superior to those obtained in hospital practice, as the mortality rate was 39.2 per cent. as compared with 60.3 per cent. in hospital cases. Satisfactory as the above results are, it must be noted that the serum was not always applied under the best or even favourable circumstances. About half the number of patients treated were poor Goans, who whether living in their clubs or shops could hardly afford, and had practically no adequate nursing or even proper care. In spite of such disadvantages, their average hospital mortality rate was lowered by more than 20 per cent. The better class of Hindoo and Parsee patients have to some extent counterbalanced this.

As regards the class of patients treated in private practice more than half the patients were Goans and about one-fourth Hindus. Amongst Parsees only 25 cases were treated. A considerable reduction in the average mortality rate in all communi-

ties is however noticeable. The following table compares the results of treatment in hospital and private practice in the different races :—

	Hospital Patients.				Private Patients.			
	Number.	Died.	Recovered.	Mortality per cent.	Number.	Died.	Recovered.	Mortality per cent.
Europeans	1	...	1	...
Hindoos	173	114	59	65.8	50	18	32	36.0
Christians (mostly Goans)	46	18	28	39.1	119	51	68	42.9
Eurasians	1	1	...	100.00
Mahomedans	29	18	11	62.0	11	4	7	36.3
Parsees	13	8	5	61.5	25	7	18	28.0
Chinese	1	...	1	...
Jews (European)	1	...	1	...	1	1	...	100.0
Total ..	262	158	104	60.3	209	82	12	39.2

The foregoing tabulation indicates that there was a difference of 21 per cent. in favour of the private patients, as compared with the hospital cases. Whereas 75 per cent. of the former came under treatment within 48 hours of their illness, the proportion was 38 per cent. only among the latter. This then is the principal contributory factor in lowering the mortality among private cases. The mortality rate among Hindoos, Mussalmans and Parsees was correspondingly lower in the private cases, the only exception being the Goans, who had a higher rate on account of their social condition and want of adequate nursing and care.

BACTERIOLYSIS.

The *theoretical* considerations involved in the *practical* application of serumtherapy and the action of various serums have been fully discussed in the light of the recent investigations of Pfeiffer, Metchnikoff, Bordet, Ehrlich, Morgenroth, Wassermann, Behring, Von Dungern, Bulloch, Wright and others.* The various serums used in the treatment of plague are what are called, *bacteriolytic serums*, that is, that under certain specified conditions they are capable of disintegrating and dissolving the bodies of the bacilli. They require for their action, the presence of certain

substances within the body of the patient called *Alexines* or *Complements* which under the stimulus of the infecting agent are elaborated in the blood, especially in the white blood corpuscles or leucocytes. And it is this combination of the active principle of the serum – called *immune body* or *amboceptor* with the *complements* that brings about bacteriolysis. The presence of both is absolutely necessary for the process ; either alone is useless. This disintegration of the bacilli liberate the toxins contained in their bodies, which have to be neutralised and eliminated from the system before complete recovery can take place. If the serums were also capable of combining with and neutralising these toxins, they would then be possessed of *antitoxic* properties as well. But inasmuch as the various serums used for the treatment of plague are but feebly anti-toxic, it is probable that the system itself supplies the deficiency by producing antitoxins, which within certain limits neutralise the toxins and prevent their combination with the tissue cells of the body. So long as the infection is moderate, the serums are able to cope with the resulting toxæmia. But experiments on animals have demonstrated that a certain degree of infection having been reached, it is of no consequence however how much serum is given ;—the result is the death of the animal. Such has also been our experience in man. In septicæmic, pneumonic and grave bubonic cases, massive doses of the serum, although they have prolonged life, have been incapable of curing the patient. It must therefore be clearly understood that there is a limit beyond which the anti-plague serums cannot act. And even in grave infections just short of this, it is not always possible to bring round the patient, because the toxæmia produced by the resulting action of the serum, is so intense and so difficult of neutralization and rapid elimination. There supervenes a new phenomenon that is fatal to the patient, *viz.* the combination of the toxins with the nerve and other important tissue cells of the body producing profound changes in the system. This result is indeed to be deplored, but it is a fact that has to be recognized. Where nature acts independently of art—in those instances where plague patients recover without the aid of serums—the process of overcoming the infection is the same and both the substances requisite to bring about bacteriolysis are produced in the blood of the patient. But there, too, whilst every plague bacillus in the body may be destroyed, the risk of toxæmia exists, but not to the same extent as where serums are used, because nature unaided is not able to disintegrate the bacilli, if the infection is grave and the patient usually dies before complete bacteriolysis can take place. This toxæmic condition has been clinically described as Plague Marasmus.

* Report on the Treatment of Plague with Prof. Lustig's Serum during 1900-01 submitted to the Municipal Corporation for the city of Bombay. Also *vide* The Treatment of Plague with Prof. Lustig's Serum, by the author, 1903,

PLAGUE MARASMUS.

Plague marasmus occurs in two forms, the acute and the sub-acute. It shows itself about the time the patient is getting apparently better—about the eight or tenth day. Considerable improvement in his general condition, the pulse and temperature almost normal, the bubo either small, hard, and getting gradually absorbed or just suppurating; and the body free from living plague germs, are the antecedent conditions. In the course of a day or so, or even during a single night, a sudden change is noticeable in the patient. The face becomes pinched and hollowed out from rapid wasting and shrinkage of the adipose and muscular tissues; the bones and prominences start out from the face; the eye-balls sink; the look becomes vacant and he lapses into a condition of semi-stupor from which he can be roused with difficulty. Speech becomes inaudible, and reduced to a whisper; the patient moans occasionally and does not like to be disturbed. The decubitus is dorsal. The pulse, a few hours before so hopeful, becomes thready, and the extremities cold. There is great prostration and general heavy condition of the limbs, which become almost leaden, and paresis of the muscles of deglutition may supervene making feeding difficult. Simultaneously with the above symptoms, the body becomes intensely icteric. The conjunctiva and nails, become yellow; the skin of the same hue, and all the excretions highly charged with bile. There is not much rise of temperature at first, unless there exists at the sametime some secondary infection or deep suppuration. The patient remains in this condition for a day or two and then the stupor becomes intensified, the pulse weaker and weaker, the wasting increasing considerably till the extremities and trunk are involved. The reflexes are abolished; glosso-labio-pharyngeal paralysis sets in and so also polyneuritis, if life is prolonged. The cornea becomes glazed, and either keratitis or panophthalmitis result. The decubitus may now become lateral with the knees drawn up, and the legs flexed over them. The temperature steadily rises and when death supervenes within six to eight days from the onset of the above symptoms it may be as high as 106° - 107° . All these symptoms indicate profound intoxication of the system. In one of the foregoing tables the proportion of marasmus in patients treated with the serum has been given as about three times as much as in those without, and that is but a logical sequence of the use of the serum. For whilst nature unaided can produce disintegration of the bacilli in only a few of the grave cases, serum must do so in a large proportion.

The same phenomena are observed in cases not treated with the serum, but as stated above in lesser proportion and they supervene if a large or even moderately sized bubo gets rapidly absorbed and disappears within a day or two, thus surcharging the

system with the liberated toxins. The same train of events follow as in the serum cases, and the fatality is always the same. In the 262 serum cases, 19 cases of acute marasmus were observed as against 13 in 766 non-serum cases. Not one of them however recovered.

In the sub-acute form, all the above symptoms exist but they develop very gradually after about a fortnight's illness, and last much longer. Whilst in the acute form, the patient dies within the third week of illness, the sub-acute form may extend to over six, eight or even ten weeks. The condition of the patient is then extremely pitiable. The wasting progresses over the whole body, all the flesh practically melts away, and the patient is reduced to a skeleton. Trophic changes in the eye supervene and sight may be totally lost through panophthalmitis; as also in the bones and joints which swell; ulcers and bed-sores form in spite of every care and attention; the power of speech and deglutition may be completely lost. The reflexes are abolished; the urine and fæces are voided involuntarily; the saliva dribbles from the angles of the mouth, and as the secretions of the throat and lungs cannot be expelled, they accumulate in the throat and almost choke the patient. Glosso-labio pharyngeal paralysis and polyneuritis supervene. The muscles become contracted, and every movement becomes painful. The patient lies doubled up, a dull, shapeless, wasted being; there is no adequate response to even strong stimuli and all that he can express in reply to calls is a groan or whine, unintelligible and scarcely human. At times, there is a vacant stare in the eye, but there is no recognition. He can hardly be said to live, but exists, until merciful nature comes to his aid and ends the misery. Here and there a recovery may be possible, but almost all such cases end in death. Convalescence is extremely prolonged, and it may take four to six months before the patient can move about. In other instances, the after-effects last for years, and the patient is never himself again as defects in speech and power of mobility become almost permanent. In the serum group 8 such cases were observed, and in the non-serum 13. There were 2 recoveries in the former and one in the latter.

Between these two forms of marasmus, there exist a few cases who may be said to be on the borderland of marasmus. They appear to be about to merge into it, when improvement sets in and they recover, though recovery is tardy. In such instances the toxæmic condition is just enough for the system to cope with and no more.

It will be observed that out of 53 cases of marasmus, but three recovered. The only way in which it would be possible to save such would be by the use of an *antitoxic serum* to supplement the action of the *bacteriolytic serum* so as to completely antagonise the living virus, and neutralise the products of its disintegration. Such a serum is still a desideratum and until one is discovered or until both properties are combined in a single serum, it cannot be said that the problem of successful serum-therapy of plague has been solved.

WHEN IS THE SERUM MOST EFFECTIVE ?

The general consensus of workers in serum-therapy is that the earlier the serum is used, the more effective it is. In diphtheria, the mortality in cases treated on the first day of illness has been reduced to almost nil, after which it rises, but quite out of proportion to the duration of illness. The same has been our experience in plague. The advantages of early treatment are so manifest that it is nothing short of criminal to delay or withhold the serum, even if a positive diagnosis be not made. It is no use waiting to see such an acute and fatal disease fully develop and thereby endanger the chances of recovery. One or two injections of serum not only do no harm, but should the patient be suffering from plague, cut short the disease. The results of early treatment are so satisfactory that if patients are treated on the first day of illness, the disease is practically arrested and its normal duration of 8 to 10 days reduced by half or even less, and they are declared out of danger by the fifth day, if not earlier. The whole course of the disease becomes thus modified : serious complications of the nervous and circulatory systems—so fatal in plague—are averted ; the temperature is rapidly controlled, the bubo becomes absorbed, and recovery is rapid. Although patients treated on the second day do not respond to the same extent they even are better off than those treated on the third day or later. It has to be recognized, however, that the ratio of fatality bears no relation to the difference in the period of treatment. It is not possible to influence the course of the disease in patients treated on or after the third day, although more do recover. But on the whole, convalescence is more readily established, and recovery is also proportionately more rapid. The subjoined comparative statement confirms the above conclusions. The proportion of early cases is greater in private practice as is but natural for very few early cases are brought to the hospital, (unless the patients

are very ill) on the first-day of illness. It was 50·0 per cent. among them against 7·2 per cent. only in hospital cases.

Duration of Illness.	1897. Yersin, Simond and the German Plague Commis- sion.				1905 and 1906. Maratha Plague Hospital.				1904-05-06. Patients in Pri- vate Practice.			
	Number.	Died.	Recovered.	Case Mortality per cent.	Number.	Died.	Recovered.	Case Mortality per cent.	Number.	Died.	Recovered.	Case Mortality per cent.
1st day	39	13	26	33·3	19	9	10	47·3	104	29	75	27·8
2nd „	71	37	34	52·1	83	50	33	60·2	68	29	39	42·6
3rd „	42	20	22	47·6	87	59	28	67·8	27	18	9	66·6
4th „	16	11	5	68·7	42	20	22	47·6	4	2	2	50·
5th „	4	3	1	75·0	21	13	8	61·9	6	4	2	66·6
6th „	1	1	...	100·0	7	4	3	57·1
7th „	3	3	...	100·0
Total.	173	85	88	49·1	262	158	104	60·3	209	82	127	39·2

The above statement indicates that cases treated on the first day of illness had the lowest mortality rate and that 104 cases so treated in private practice had a mortality rate of only 27·8 %. It increases with the duration of illness, being higher in the second-day cases and highest on those treated on the third day. Cases treated on the fourth day exhibit a somewhat lesser mortality ; the probable explanation of this lies in the smaller number of observations, as also in the fact of the most acute cases having succumbed on the day previous.

The disproportion in the rates of mortality between hospital and private cases is exceedingly well marked. Contrast for instance the 47·3 % in the former as against 27·8 in the latter, a difference of nearly 20 %. Similarly there is a difference of about 18 % in favour of the private cases treated on the second day. It is only in the cases treated on the third day that the rates are about equal, indicating that whether private or hospital cases, the virulence of the disease is very great on the third day of illness, and that social conditions do not modify the essential characteristics of an infection like plague. The above results, if tabulated together, tell the same tale, and

show that the mortality rate in cases treated on the third day of illness is about double of that in the first day cases.

Duration of Illness.	Number.	Died.	Recovered.	Case Mortality per cent.
1st day	162	51	111	31·4
2nd „	222	116	100	52·2
3rd „	156	97	59	62·1
4th „	62	33	29	53·3
5th „	31	20	11	64·5
6th „	8	5	3	62·5
7th „	3	3	100·0
Total ...	644	325	319	50·4

Apart, however, from the better recovery rate under the serum treatment, there is early convalescence also. Two causes contribute to it, *viz*:—fewer complications during convalescence and lesser suppuration of the buboes. There is almost uninterrupted recovery when buboes do not suppurate: if they do the proportion is much less than in cases treated without serum.*

DOSAGE OF THE SERUM.

To determine the exact dose of the serum, or the probable quantity required in any case is a question beset with many difficulties. The complex nature of the affection, its great virulence and high mortality, the early septicæmia, its rapid course, and the presence of multiple foci of systemic infection—all are closely inter-related with the question—apart from the late stage at which patients usually resort to treatment, especially in hospital practice. That the disease is complex in its nature and requires two distinct processes,—bacteriolytic and antitoxic—before recovery can take place is an accepted fact. That in its virulence and fatality it equals if not surpasses cholera is equally well-known. No better proof of this could be had than that provided by the official statistics of Bombay. During the three years 1904, 1905 and 1906, 44,119 attacks and 38,566 deaths were recorded from the disease, equivalent to a case mortality rate 87·41 per cent. If hospital patients who had a lower mortality rate are excluded, and a certain proportion of cases,—unrecognised or unreported,—added to the above, it would not be too high to assume the normal mortality at 90 per cent.—the actual figures, excluding the latter, being 89·20, 88·43 and 90·34 per cent. respectively, for the above period. That a

* *Vide supra*.

large proportion of the patients admitted into the hospitals is septicæmic is beyond doubt as shown by our previous observations, subsequently confirmed by Greig and the Plague Research Commission. About 55 to 60 % have been found to be septicæmic, and therefore beyond all hope, although an occasional recovery especially under the serum treatment is possible. Almost all succumb within 48 hours of admission*. That the disease is rapidly fatal, by far the largest number of deaths occurring between the fourth and sixth day of illness is sufficiently recognised—indicating as it does the almost absolute inability of the system to cope with such a grave infection, and its failure to elaborate enough bacteriolysin and antitoxin to overcome the same. That such is the case is well brought out in the postmortem room, when grave degenerative and necrotic changes in the tissues and organs demonstrate the effects of the toxins liberated by the disintegrated plague bacilli. And finally that more than one focus of systemic infection exists in almost every case, points to the gravity of the infection.† A patient with a large single apparent bubo has far more chances of recovery and comes more readily under control, than one in whom a chain of buboes extends either upwards or downwards; the gravity in such, whether situated in the neck, pelvis or abdomen, the upper or the lower extremity is indeed not small. The late stage at which more than 90 per cent of hospital patients are admitted—from the third to the sixth day—is one of the principal factors adversely affecting the results of the treatment.

Under the above circumstances the determination of the exact dose of the serum or of the number of injections necessary in a given case would appear to be a matter of practical difficulty. Each individual case must be governed by its existing factors, and it is only by their intelligent appreciation and the proper adaptation of the means to the end, that any exact course could be laid down. Indefinite and indecisive as such a conclusion would appear at first sight to be, in spite of our fairly extensive experience with the subject, it is but no more than justified by it, as also by the limitations imposed upon us by the extreme virulence of the disease. At the same time however, it is possible to lay down certain broad outlines along which the course could be steered with safety and cases successfully treated.

* Drs. Alfons Mayr and Berestneff found that among 1,014 admissions at the Maratha Hospital (1902) 437 that is 43·07 per cent. were septicæmic; not one patient recovered. At the Authur Road Hospital the proportion was 43·79 per cent. with but 2 recoveries. The Plague Research Commission examined 94 patients, 55 of whom, that is 58·57 were found to be septicæmic: only 2 patients recovered, one of whom had septicaemia on the second day of illness and the other, no fewer than 500-600 plague bacilli per c. c. of blood. Both the patients were treated with Yersin-Roux Serum.

† *Vide* The Treatment of Plague with Prof. Lustig's Serum by the Author

If patients are treated on the first day of illness, it is not only possible to cut short the normal duration of the disease, from ten to fifteen days—but at the same time to avert the risk of grave complications and to considerably hasten recovery—subject however to the absence of septicæmia or rapid extension of buboes or early cardio-vascular paresis—all so dangerous and known to complicate grave infection even within a few hours. The first injection should be of 100 c. c., it should be followed up within 6 to 8 hours by another, and then if necessary by a third. Thereafter on the abatement of fever and general and local improvement, one or two small injections of from 20 to 50 c. c. should be given at intervals of 24 hours. Should there be no improvement in the condition of the patient, in spite of the above injections, the infection must be presumed to be grave and blood examination would demonstrate septicæmia. Should fresh buboes appear, the injections must be continued until they subside. In any case it is never safe to discontinue them until the complete subsidence of fever and amelioration of other symptoms.

In patients treated on the second day of illness, it is also possible to reduce the duration of the affection to seven or eight days. The injections should be given as above or one morning and evening ; but both the number of injections and the total quantity injected will be in excess of that required on the first day of illness.

On and after the third day there is usually no possibility of bringing about any reduction in the normal period of the illness, and all that one can expect to do is to tide the patient over it—until recovery ensues. In the absence of septicæmia or of extension of lymphatic infection or of grave cardio—vascular paresis, the system already elaborating nature's curative agencies, requires further extraneous help and that the serum provides. It can be best rendered by giving one or two injections of 80 to 100 c. c. within 24 hours, and following these up by a gradual reduction to 60, 40, and 20 c. c. respectively, until amelioration takes place. The development of new buboes, or of lung complications would necessitate the continuance of injections, and eventually should septicæmia be present, it becomes virtually a race between the plague bacilli and the serum in which almost always, the former wins with but few exceptions.

Patients treated on the fourth day may be similarly treated, but thereafter, the serum does not appear to be effective, as the majority of patients are too gravely affected and being practically moribund, succumb by the sixth day. Those in whom amelioration may be just setting in,

might require a little aid, but in ordinary course, especially if uncomplicated, recovery is probable in those who survive over the sixth day, barring of course such accidents as sudden heart failure that are so inseparable from the affection.

The above indications might be summarised as follows :—

First-Day Cases—One injection of 100 c. c., followed by a second of same quantity after six to eight hours and then if necessary by a third after a similar interval. Subsequently one or two injections of 20 to 50 c. c. every morning :—

- (1) 100 c. c., (2) 100 c. c., (3) 100 c. c.,
(4) 50 c. c., (5) 20 c. c.

Second-Day Cases—As above or one injection morning and evening for 2 days and subsequently one injection every morning ;—

- (1) 100 c. c., (2) 100 c. c., (3) 80-100 c. c.,
(4) 80 c. c., (5) 60 c. c. (6) 40 c. c., (7) 20 c. c.

Third and Fourth-Day Cases—The first two injections may be at interval of 12 hours and subsequently one injection every morning :—

- (1) 100 c. c., (2) 80-100 c. c., (3) 60-80 c. c.,
(4) 45-60 c. c., (5) 20-40 c. c., (6) 20 c. c.

The quantity of serum required for cases of average severity with large single buboes, *e. g.* the femoral or axillary or cervical will therefore vary as under :—

First-day Cases	200-350 c. c.
Second-day Cases	300-400 c. c.
Third and Fourth-day Cases...			300-500 c. c.

These are full adult doses ; for children upto 12 years, half the above quantity would suffice and for the very young (between 1 and 3 years) 10 to 20 c. c. should be the limit of each injection. It cannot be sufficiently reiterated that the frequency of injections and the amount of serum required, in a given case must be carefully and intelligently adapted to its requirements and that no hard and fast rules should be laid down. Where the infection seems to be moderate and yet persistent as in mesenteric and deep abdominal infection, daily injections may be necessary for any period upto the twelfth or even fifteenth day of illness. Should they be stopped too early, relapse is the rule, and fatal results are not infrequent. Abrupt stoppage of the serum under any circumstances is not desirable as it is not free from risk. It is therefore advisable to err on the safe side, and to use rather more than less serum.

INSTRUCTIONS FOR SERUM INJECTIONS.

I The Serum.

1. Yersin-Roux Serum * is put up in phials of 20, 40-50, and 100 C. C. It is perfectly sterile ; the presence of sediment is no contra-indication to its subcutaneous use.

II The Syringe.

1. The syringe in general use, is of 20 C. C. capacity and is provided with needles and a india-rubber draw-tube. The syringe, needles and the draw-tube should be boiled for 15 minutes before use in 3 p. c. carbolic lotion and if well rinsed out with the lotion after use could be re-used the same day.

They should be boiled every morning before use. All the parts should be kept scrupulously clean and free from rust. The needles could be separately re-sterilised in boiling parrafin with Kapadia's lamp†.

III Method of Injection.

1. The method of using the syringe, of filling it through the draw-tube and of injecting is as follows :—

(a) Prepare the part where injection is to be made—as near as possible to the bubo—with soap and water ; sterilise it with carbolic (3 p. c.) or sublimate (1—1000) solution or equal parts of absolute alcohol and ether ; place some cotton soaked with any of the above over the spot selected for the puncture.

(b) Attach the draw-tube to the nozzle of the syringe and draw up the serum from the bottle till the syringe is full, exclude all air bubbles as far as practicable. Withdraw the tube from the serum bottle and fix the needle to its free end, and insert the needle subcutaneously as close to the bubo as possible, taking care not to puncture it and inject the serum slowly. As soon as the syringe is emptied, detach the draw-tube from the needle, leaving the latter in situ, refill the syringe as before and inject again. Repeat this procedure until the full quantity has been injected ; then withdraw the needle and seal up the puncture with collodion flexile and cotton wool. In case there should be much pain or tension after injecting a certain quantity at a given spot, withdraw the needle, seal up the puncture, and make a fresh puncture at some distance.

(c) Give the subsequent injections on the same limb and either surrounding the bubo or at a lower level depending upon the tension. Should the limb or part be very tense, then inject

* The Serum is obtainable from Mr. M. A. J. Noble, of Patell Street, Fort, Bombay.

† Obtainable from the Bombay Bacteriological Laboratory, Parel.

on the flank or opposite side. In cases with cervical buboes the first injection should be made in the neck and the subsequent ones as close to the neck as possible.

(d) No particular local treatment for the buboes is required in cases treated with the serum. It is always preferable to keep a cold compress of cloth, lint or cotton wool over the seat of injection. If there is much pain or tension an ice-bag soon relieves it. The buboes become hard mobile and painless after one or two injections of serum.

GENERAL TREATMENT.

The present volume being not a treatise on plague, any detailed consideration of the general treatment of plague would be out of place. The following main indications might be followed out in all cases treated with the serum :—

1. *Control of Temperature* :—Avoid all antipyretics—general or local—coal-tar or other; they are worse than useless, nay harmful. Diaphoretics do no good. Remember that the disease has a definite duration and that no amount of antipyretics or quinine could influence its course or lessen the fever. Constant application of the ice-bag or ice-cap, sponging and wet pack (to the trunk only) should be utilised to control the fever.

2. *Cardiac Treatment*.—As in almost every instance plague kills at the heart and as grave cardio-vascular paresis sets in early in many cases, even within a few hours, all efforts should be directed to keep up the circulation. After numerous observations it has been found that alcohol as a heart stimulant is not only useless, but positively dangerous. Avoid therefore alcohol in any shape. The best remedy for the purpose is adrenalin chloride solution (1-1000)* administered in doses of 10 to 30 minims every 2 hours. In grave cases 20 minims can be exhibited hourly.† It is best to administer it by itself or in normal salt solution (sodii chloridum 3 grs. to 1 oz. of sterilized water.) It can be used subcutaneously, also in doses of minims to 10 to 20. Extract Renaglandin‡ can be substituted instead. These could be supplemented with spartein sulphas in $\frac{1}{2}$ grain doses in combination with liq. strychnine, minims 3 to 4 given alternately. For general prostration, nervous or circulatory, the following is useful, subcutaneously in doses of minims 20 every 2 or 3 hours or even oftener :—

R/

Camphor	2 parts
Ether sulphuric	3 „
Ol : Olive	7 „

* Manufactured by Parke Davis & Co.

† *Vide* articles on the subject by the author in the Indian Medical Gazette, April 1905 and February 1907.

‡ Oppenheimer's.

3. *Delirium*.—This very often taxes the strength of the patient, and the skill and patience of the physician. When mild, the bromides, 10-15 grains with tinct. hyoscyami in doses of 30 to 60 minims administered two hourly in succession, generally control it. Chloretone, grains 10-30—is very useful and not depressing. If violent, hyoscine hydrobromate ($\frac{1}{100}$ to $\frac{1}{8}$ grain) may be given subcutaneously, as required, (not more than twice) in the course of a single night. The pulse however needs careful watching. It is preferable to use hyoscine even with a weak pulse rather than allow the patient to die of heart failure from violent delirium. If it is carefully used, the pulse improves remarkably. Where hyoscine fails, morphia must be the last resort, if the pulse be good, otherwise the patient never gets over its effect. It is best therefore to eschew it.

4. *Lung Complications*.—They should be treated on general principles; counter-irritation to the back, poultices or anti-phlogistine or thermofuge applications will be needed. If there be hæmorrhage, calcium chloride in 15 grain doses every 3 hours is very effective even in plague pneumonia. Ammonia, senega, squills, &c. should be given to encourage expectoration.

5. *The State of the Bowels*.—It should be looked into. Free purgation at the outset often brings about collapse in many instances. A small dose of calomel or some other gentle aperient followed up by an enema of soap and water with or without turpentine serve all the requirements. If vomiting is persistent, preparations of bismuth will be necessary together with absolute rest to the stomach for a few hours. Tympanites necessitates the absolute stoppage of all milk; turpentine or salol with ol. month. pip. by mouth, turpentine enemata or a rectal tube inserted high up and retained for a few hours, generally overcome this complication. Diarrhoea should be treated on general principles avoiding preparations of opium.

6. *Nourishment*.—Milk, well diluted with arrowroot or sago congee, sanetogen or plasmon, coffee, barley and aerated waters should form the main basis of nourishment until the patient tides over the acute stage. Avoid all meat juices, extracts or essences if patients are not accustomed to meat diet in health. Remember that the patient in the acute stage of such a grave infection does not need, nor can he digest much nourishment in large quantities; do not therefore overload the stomach.

7. *Complications*.—Should be treated on general principles.

AFTER-EFFECTS OF THE SERUM TREATMENT—THE SERUM DISEASE.

A close similarity exists between the after-effects of diphtheria antitoxin as described by Dr. Rolleston *and those observed

* Oppenheimer's.

after the use of anti-plague serum. He mentions rashes, joint pains, abscesses and hyperidrosis (profuse secretion of perspiration) ; and they all appear after injections of anti-plague serum with varying frequencies :—

(a) *Rashes* :—Three types of rashes or erythema have been observed; the most common being circinate erythema, next in order, scarlatiniform erythema, and the least frequent, the urticarial type. Circinate erythema is the most common and spreads outwards in all directions from the seat of punctures, covering well-defined areas with marked circinate margins which are deeper in colour, than the diffuse erythema they surround. It does not occur on parts of the body free from punctures of injections. A slight rise of temperature generally accompanies it, but there is no systemic disturbance. Local irritation from pruritus causes annoyance which subsides within three or four days under cold compresses of boric acid.

Scarlatiniform erythema, more often general than local, comes next in order, but a long way behind. There is considerable systemic reaction, the temperature is raised, and thick eruption like that of a severe attack of scarlatina or measles develops. It is rather faint at first, but becomes gradually intensified. There is intense pruritus and it leads to restlessness and insomnia requiring the use of sedatives and even narcotics. Although the sudden change in the condition of the patient looks alarming, there is no cause for anxiety as the erythema gradually fades away in the course of four to six days.

Urticarial rashes are extremely rare ; they are localised to the areas surrounding the seat of punctures or to the limbs. In my own case, wheals upon wheals with considerable œdema surrounding them appeared on both the upper extremities, as the injections had been given in the axilla and on the arm. They disappeared at one spot on the application of ice, and reappeared at another within a few minutes. There was no constitutional disturbance and no rise of temperature, but intense pruritus which was relieved by the application of ice. The eruption lasted for about two days only and then disappeared.

The rashes appear within one week of the injection of the serum and are of varying degrees of intensity. Hardly any patient escapes, and in all those cases who recovered under the serum treatment they were recorded. It is indeed curious that the rashes as well as joint pains should affect those classes of people more who usually take meat than the strict vegetarians. Boric acid (dry or in compresses) and ice, generally allay the pruritus. Rolleston recommends menthol 1 drachm to paraffin alb. molle 1 ounce.

(b) *Joint Pains*.—Joint pains generally develop after the subsidence of rashes. There is effusion and swelling of the joints with intense pain, fever and difficult mobility. All the joints are not simultaneously affected, but by turns; after pain and swelling have subsided in one joint or set of joints, they appear in another and then in a third until practically hardly any principal joints of the body escape. The degree of pain and the number of joints affected bear no relation to the amount of serum injected. In my own case, for instance, although only 400 c. c. was injected, the joints were affected on both sides in the following order:—Phalangeal, metacarpal and wrist joints, then the elbow; the shoulder joints escaped although the serum was injected so near to them; then the metatarsal, tarsal and ankle joints, followed by the knee, and lastly the temporo-maxillary joint on one side. Cases where so many joints are attacked, are infrequent. The wrist and elbow or ankle and knee are the joints usually affected. Joint pains occur in about 25 per cent. of those who recover under the serum treatment, and though not dangerous to life, cause much pain and misery by preventing sleep and retarding convalescence. They are however amenable to treatment, and leave no after-effects. Local applications of glycerine and belladonna, methyl-salicylate, mesotan or betul-ol and internally an alkaline mixture with or without salts of salicylic acid or aspirin are the means to control it. Pains in muscles and fascia are infrequent; they aggravate the joint pains; movement becomes extremely painful and practical immobility of the limbs may temporarily result.

Preventive Treatment of Serum Disease.—Netter recommends the use of calcium chloride as a preventive of serum disease. He administers 15 grains after each injection and for two days following, after they are stopped. This procedure has been adopted during the epidemic of 1907, and with good results.

(c) *Abscesses*.—Dr. Rolleston holds that abscesses after serum injections are due to discreditable lack of asepsis. In hospital practice, however, dealing with not overclean native patients, it is so difficult to prevent them. In spite of aseptic serum, aseptic instruments and as thorough a cleansing of the skin as is possible, abscesses occasionally occur. It is practically impossible to render the skin thoroughly aseptic in many cases, and the more so if the skin is tough and horny. Oft times gaseous abscesses form which if incised early and appropriately treated do not give rise to any difficulty. They give no trouble in healing which is fairly rapid. They occur at varying periods after injection, but generally within three weeks. No infection with the *bacillus aerogenes capsulatus* has been noticed among the cases treated.

(d) *Hyperidrosis*:—Profuse secretion of perspiration has been noticed after intravenous injection, and so also coryza with excessive nasal secretion, and copious lachrymation. With subcutaneous injections, however, such is not the case, although during convalescence in some patients it is to be occasionally met with. With increasing strength, it gradually disappears.

OBSERVATIONS AT POONA, 1906.

The serum treatment of plague came into vogue at Poona during the epidemic of 1906 after one patient had been successfully treated by Lieut.-Colonel Burke I.M.S., and Dr. Erasmus Dias in consultation with the author. It was readily taken up by the profession, official as well as non-official, and was also used at the General Plague Hospital. In spite of the fact that in several instances the treatment was adopted among patients scarcely suitable, the results were found to be satisfactory and coincided with those obtained at Bombay. Dr. Anklesaria treated 56 patients at the General Hospital, of whom 34 died and 22 recovered, the case mortality being therefore 60·71 % as compared with 60 % among 270 cases treated at the Maratha Hospital, Bombay. Major G. Thomson I. M. S., Captain Sylvester Bradley, R.A.M.C., Drs. Modi, Bilfodiwalla, Gokhale, Dias, Bharucha, Shikhare and Soonderlal Modi treated altogether 62 patients, all of whom were private cases with the exception of 11 treated by the first two in the regimental and cantonment hospitals. There were 24 deaths and 38 recoveries among them, equivalent to a case mortality rate of 38·7 % as compared with 39·2 % among 209 private cases at Bombay. The results in both these series of cases exhibited a remarkable coincidence. The treatment was conducted on the lines laid down in my report describing the results of the treatment at the Maratha Hospital during the 1905 with the exceptions noted below. The results of the cases treated by each observer will be found in the summary at the end of the volume.

Remarks :—From the details kindly furnished by the above observers, to whom the thanks of the author are due, it appears that in clinical effects, as well as in other particulars the action of the serum was found to be similar to what was noted by the observers at Bombay. Among 60 patients who recovered, the buboes did not suppurate in 30, a somewhat lower ratio than at Bombay. The “Serum Disease” (erythema and arthritis) was not so evident at Poona, as the majority of patients were strict vegetarians, in whom those complications do not appear with much frequency. About 15 patients only suffered from it. Secondary pneumonia was observed in 6 patients, 5 of whom recovered and one died. Two patients who had been inoculated with Haffkine’s prophylactic, six and ten days previous to the attack, were treated with the serum, and both recovered.

Among the fatal cases, two were septicæmic, and one of pneumonic plague. The serum was prematurely stopped in four cases. Five had practically no care or nursing. One patient was pregnant and succumbed after premature labour. Another died from marasmus and meningeal symptoms after 2 months. One patient was unconscious, but recovered consciousness after the first injection of serum, and was able to make her will, but succumbed thereafter. One was a case of second attack of plague after an interval of four years.

Dr. Anklesaria reports that out of 56 cases treated by him 30 were treated on the 3rd day of illness, 17 on the 4th day and the rest thereafter. There was thus not a single first or second day case among them, showing that Poona's experience in hospital practice is identical with that of Bombay. As regards the number of injections and the quantity of serum used, it was more liberal in private than in hospital practice. Dr. Anklesaria's average with the above cases was 228 c.c. per patient as compared with the average of 310 c.c. at the Maratha Hospital. The hospital mortality at Poona was 65 % among 1717 patients who were under ordinary treatment. That may be due either to the type of the disease being less virulent than at Bombay or to the most serious cases having died off before removal to the hospital or to a somewhat better class of patients than those generally coming under treatment at Bombay. But the fact that the average mortality rate was 93.5 % during the epidemic, shows that the last two factors were probably responsible for the lower hospital mortality. Had the serum been used somewhat more freely under the above comparatively favourable circumstances, the results would have been still better. Major G. Thomson I. M. S. was far better situated with regard to his patients as they were all first day cases, but he appears to have used too small doses. Seven of his patients were privates from his regiment (104th Marathas N. I.) and as they were all seen within a few hours of illness he could have obtained better results, instead of only 2 recoveries among 7 cases, had he used the serum more liberally.

OBSERVATIONS AT INDORE, 1903-06.

I have to express my sincere thanks to Dr. G. R. Tambe, State Surgeon at Indore, for having placed at my disposal his report on the Serum treatment as conducted by himself and some of his colleagues at Indore. The serum was first employed by him in 1903-04, when about 25 patients were treated, 13 of whom recovered. During 1906 a larger number of patients was treated. At the Indore Plague Hospital, 92 patients were treated of whom 39 died and 53 recovered, the case mortality rate being

42·3 % Among 101 private cases, there were 27 deaths and 74 recoveries, equivalent to a case mortality rate of 26·7 % These results appear to be extremely favourable, inasmuch as nowhere anything approaching to them has been recorded.

They could be accounted for either by the comparatively lesser virulence of the disease or by early treatment or by the greater efficacy of the serum. Dr. Tambe states that "the recoveries amongst general patients in the city,—not to mention those treated at the plague hospitals or registered as out patients were not less than 1,553 out of between 6,000 to 7000 attacks." The average case mortality rate would therefore work out at 74·1 or 77·8 % respectively, *i. e.* much lower than what obtained at Bombay or Poona—90·3 and 93·5 per cent respectively. The hospital mortality rate at Indore among non-serum cases was also lower as compared with Bombay and Poona :—

	No. of non-serum cases.	Case mortality per cent.	Total case mortality per cent for the City.
Bombay	2,045	75·2	90·3
Poona	1,717	65·0	93·5
Indore	309	61·1	74·1 to 77·8

The foregoing statement therefore indicates that compared with Bombay and Poona, the epidemic at Indore was of comparatively lesser virulence and in so far it must have favoured the better results of the serum treatment.

The second point to be considered is the duration of illness at time of treatment and in this instance also Indore appears to have been exceptionally favoured :—

	Proportion of first-day cases to total treated in Hospital.	Proportion of first-day cases to total treated among private patients.	Proportion of first-day cases to total treated ; Hospital and Private.
Bombay	7 p. c.	50 p. c.	28 p. c.
Poona	Nil	40 p. c.	21 p. c.
Indore	44 p. c.	83 p. c.	64 p. c.

Both among hospital as well as private cases, the first-day cases had an overwhelming preponderance at Indore as compared with Bombay and Poona. Poona had no first-day hospital cases at all. The mortality rate among the first-day serum cases stands as under :—

	Case mortality rate of 1st day Hospital cases.	Case mortality rate of 1st day Private cases.	Difference in mortality rate between the 1st and 2nd day cases. Hospital and Private.	Difference in mortality between 2nd and 3rd day cases. Hospital and Private.
Bombay	47·3	27·8	22·2 higher.	15·2 higher.
Poona.	<i>Nil</i>	20·0	32·3 higher.	9·3 higher.
Indore	31·7	25·3	13·6 higher.	3·0 lower.

Bombay, Poona and Indore all equally exhibit a mortality rate of less than 30 % among the private cases treated on the first day of illness, Poona. Indore and Bombay standing respectively in the order of merit. The milder virulence of plague at Indore is again demonstrated among the hospital cases as they had a lower mortality rate than at Bombay, the difference being 15·6 % among the first day cases, and similarly the second day cases had a higher mortality rate by 13 % than the former as against 22·2 % at Bombay. The fact that the mortality rate was lower by 3 % among the cases treated on the third day at Indore can be explained by the comparatively smaller number (21 out of 122) treated on that day. It thus appears that both as regards the virulence of the epidemic and the period when the patients came under treatment, Indore was exceptionally favoured.

There could have been no difference in the efficacy of the serum except in so far that the milder type of the disease required a correspondingly smaller dose. But looking to the doses employed and the limited number of injections given (114 patients had only one injection of less than 40 c. c.; 51 received two injections aggregating 52 c. c.; 24 had 87 c. c., and 4,112 c.c. each) the mildness of the disease is even more prominently brought to view than by the previous figures. Our experience at Bombay with such small doses has been so unfavourable, both on account of the virulence of the disease and its rapid extension within a few hours of its onset, that the small doses as used at Indore or the delay of 24 hours between two injections as practiced by Dr. Tambe would be fatal, and would hardly show any recoveries at all. We must conclude therefore that no comparison between the Bombay cases and those at Indore would be of any value.

The only cases with which they could at all be compared and to which they approach in results are these among the European patients treated at Oporto by Calmette and Salimbini. But at the same time we have to note that whilst the average city mortality was between 74 and 78 % it became reduced to 42 per cent in hospital cases and 26 in private cases—a striking difference and greater than that noted at Oporto but which is not capable of any explanation. Another point that is rather puzzling is the difference in the results between hospital and private serum cases:—

	Case mortality rate of Hospital Serum cases.	Case mortality rate of Private Serum cases.	Difference in favour of Private cases per cent.
Bombay ...	60.3	39.2	21.1
Poona ...	60.71	38.7	22.0
Indore ...	42.3	26.7	15.6

With epidemics of a more virulent type the results as Bombay and Poona show almost identical differences between the hospital and private cases, and yet strange as it may appear, the results at Indore, instead of being better, are lower by 6 per cent. After making due allowances for everything that favoured the serum cases at Indore it becomes evident that certain points remain inexplicable and neither Dr. Tambe's report, nor his subsequent communications to the author throw any light on them. The Indore results must therefore be judged on their merits as they stand.

OBSERVATIONS AT CALCUTTA. 1904-1905.

Lieut-Col. Dutt I.M.S., Dr. M. Banerjee and others have used the serum at Calcutta on a rather limited scale and from the data supplied by them to Dr. Frederick Pearse, the Special Health Officer for Plague it appears that during the year ending 30th June 1905, particulars of only 20 cases so treated could be obtained. Six of them were moribund or nearly so when injected. The treatment in almost all the cases was adopted late, the doses employed were small, and in nearly half the cases one injection only was administered. Marked and rapid change for the better was observed in six cases. The mortality rate among *all* the serum cases was 65 per cent, as against 78 per cent in hospital cases. Dr. Pearse summarises these observations as under:—

“The inference to be drawn from this limited series is that if the serum be given early in the case in full doses, and be

repeated without hesitation the chances of recovery would be greatly improved. It is tolerably certain that in cases where no improvement follows its use, there is at least no deleterious action induced. From my own experience I have formed a high opinion of its value."

OBSERVATIONS AT KARACHI.

I have not been able to obtain particulars of the cases treated with the serum at Karachi, but I believe Dr. Nazareth has treated a large number with good results and so also some other practitioners.

SUMMARY.

The observations detailed in the preceeding pages may now be fitly summarised here and the results considered on the whole I have endeavoured in the following statement to furnish as complete a list as possible of the observations made with Yersin - Roux serum upto the end of 1906 ; with the exception of the cases treated at Karachi and a few at Bombay the date of which are unfortunately not available, it may be taken as complete:—

Observers	Number	Deaths.	Recoveries.	Case mortality per cent.
1898—1904.				
Yersin, Simond, Mason, The German, Russian and Indian Plague Commissions Drs. Alfons Mayr, West and the author, (at Bombay, Bangalore, Karad, Karachi, Mandvi &c.)	570	358	212	62.0
Total. ...	570	358	212	62.0
1905—1907. BOMBAY.				
The author (at the Maratha Plague Hospital.	270	162	108	60.0
Total ...	270	162	108	60.0

Observers.	Numbers.	Deaths.	Recoveries.	Case Mor- tality per. cent.
1905 and 1906.				
BOMBAY.				
In Private Practice:—				
Dr. B. Pais	122	50	72	40·9
Dr. M. A. de Heredia	48	16	32	33·3
The Author	33	13	20	39·3
Dr. Alfons Mayer	6	3	3	50·0
Total ...	209	82	127	392
1905 and 1906.				
INDORE.				
Dr. G. R. Tambe	25	12	13	48·0
Do. do.	61	12	49	19·1
Plague Hospital staff	92	39	53	42·3
Dr. S. N. Deo.	4	1	3	25·0
„ Bhandarkar	1	...	1	...
„ Atmaram	5	1	4	20·0
„ Sarangpani	19	12	7	63·8
„ Golvelkar	1	...	1	...
Tookajirao Hospital staff	7	...	7	...
Dr. Surujparsad	2	...	2	...
Mr. Lohokre	1	1	...	100·0
Total ...	218	78	140	35·7

Observers.	Number.	Deaths.	Recoveries.	Case Mor- tality per cent.
1906.				
POONA.				
Dr. B. K. Anklesaria at the General Plague Hospital.	56	34	22	60.7
Dr. Erasmas Dias	17	8	9	47.0
„ S. H. Modi	16	3	13	18.7
Major G. Thomson I. M. S. ...	8	5	3	62.5
Dr. Erach S. Bharucha	6	3	3	50.0
„ D. S. Bilpodiwalla	4	4
Captain Sylvester Bradley R.A.M.C.	3	3
Dr. P. V. Shikare	3	2	1	66.6
„ Soonderlal N. Modi	3	2	1	66.6
„ V. C. Gokhale	2	1	1	50.0
Total ...	118	58	60	49.1
1904-1905.				
CALCUTTA.				
Dr. M. Banerjee	3	1	2	33.3
Other Practitioners	20	12	8	60.0
Total ...	23	13	10	...
Grand Total ...	1408	751	657	53.3

The foregoing statement shows a total of 1408 cases treated with the serum with a mortality rate of 53.3 per cent. If the observations made during the last two years, are separated from those of the previous years some striking results are apparent.

	Number.	Deaths.	Recoveries.	Case Mor- tality per cent.
Observations up to and including 1904.	570	358	212	62.0
Observations during 1905 and 1906.	838	398	445	46.8
Total ...	1408	751	657	53.3

The latter observations number 838 as against 570 during the previous years. While they comprise but isolated observations, conducted by different observers in small numbers at various centres, under varying conditions, and distributed over a period of seven years, the latter have the advantage not only of more systematic observation, but of having been conducted during two epidemics at three places. And further, whilst the previous ones laboured under the disadvantages incidental to all new lines of treatment, the latter have gained by the experience obtained in the serum-therapy of plague with other serums besides the one under consideration. Greater confidence in its utility and boldness on the part of observers would therefore explain the better results of the later observations.

Another point that the above statement brings into view is the disparity in the results between hospital and private cases owing to the greater preponderance of first and second day cases among the latter, apart from their better social condition :—

	No.	Deaths	Recoveries	Case Morta- lity per cent.
Hospital Cases	436	240	196	55.0
Private Cases	402	153	249	38.0
Total ...	838	393	445	46.8

The difference of nearly 17% between the two is a striking testimony of the advantage of early treatment, which is still better demonstrated by the following tabulation of 966

patients according to the duration of illness when they came under treatment :—

Duration of illness					Number.	Deaths.	Recoveries.	Case mortality per cent.
1st day	311	90	221	28·9
2nd "	292	146	146	50·0
3rd "	219	131	88	59·8
4th "	89	49	40	55·6
5th "	38	26	12	68·4
6th "	14	8	6	57·1
7th "	3	3	...	100

The above table indicates that the lowest mortality was observed among patients treated on the first day of illness, that it increased from 28·9 to 50·0 % among those treated on the second day and that it was more than double among those treated on the third day. Thereafter some irregularity in results is noticeable, but that is due to the comparative smallness of the number of observations on the later days.

Finally the racial distribution of the patients and their incidence of mortality are indicated by the following analysis of 800 cases :—

Races.					No.	Deaths.	Recoveries.	Case Mortality per cent.
Europeans	10	2	8	20·0
Parsees	55	19	36	34·5
Mahomedans	116	48	68	41·3
Native Christians (mostly Goans).	181	75	106	41·4
Hindus	434	225	209	51·8
Chinese	1	1
Jews	2	1	1	50·0
Eurasians	1	1	...	100·0

The incidence of mortality was the lowest among European patients, but the number treated was too small. Of the other

communities, Parsees stand next to Europeans with the mortality rate of 34.5, and then Native Christians and Mahomedans with 41.4 and 41.3 per cent respectively and lastly Hindus with 51.8%. These results bear a corresponding ratio to the natural mortality from plague among these races.

CONCLUDING REMARKS.

A careful and impartial survey of the whole field of serum-therapy in plague, having regard to the limitations imposed by the nature of the affection, must perforce lead to but one conclusion, viz., that it is the only treatment capable of saving a larger proportion of lives in a certain class of patients. That it cannot favourably influence all types of plague, or even the malignant forms of bubonic plague must be recognised. As also the fact, that in *hospital practice*, where more than half the number of admissions are advanced too far for any beneficial influence, it must be of comparatively limited value. In every case of plague, there is constant disintegration and reproduction of the plague bacilli. Should the system be not capable of producing enough antitoxin to neutralise the toxins liberated by this process, they combine with the tissue cells, a combination that is fatal to the individual. Greater success is possible only in those instances, where such combination could be forestalled and that can only happen where early treatment is resorted to. That unfortunately is not possible in hospital patients. And again the great disparity between the results of treatment on the first as compared with those of the second day, should not be overlooked, indicating as they do the extreme gravity of withholding the serum even for a few hours. Under such circumstances, is it to be wondered at that in hospital practice, we have not been able to do more than to save about 10 to 15 more lives out of every 100, by the use of the serum? This result, be it remembered, is obtained in a disease that carries away about 90 people on an average out of every 100 attacked. From my long and intimate connection with plague, and its serum-therapy I am inclined to conclude that, for the present at least, the above must be considered to be the limit of our success. It has been impressed upon us, that were the serum used intravenously in preference to the subdural method, the results would be infinitely better. No doubt they would be, were the circumstances favourable for its general adoption, and the material with which we have to deal, different. So long, however, as we have to work under conditions as hitherto obtainable, I do not think, better results are possible unless, indeed it be that we obtain a serum combining *both anti-toxic and anti-bactericidal properties*. Then, perhaps, we could save a few more lives. To expect miraculous cures or

even brilliant results, in a disease like plague is simply futile, and hardly in accord with our knowledge and experience, as well as our successes and failures, in the treatment of other grave infections.

The whole aspect of plague serum-therapy, however, alters when applied under different, and in most cases, more favourable circumstances—that is in private practice. Here the patients belong to a better class of society, are better housed and better fed. They come under observation early, and unless there is gross carelessness or the symptoms masked, plague is recognised early and treated equally early. That the disease does not become altered, or its characteristics change, because the patient happens to be in a better social position is demonstrated by the great disparity between the results of the first day as compared with those of the second day treatment and once again it emphasises the cardinal fact that if good results are to be obtained from serum-therapy the patients must be treated on the first day of illness.

I consider the results obtained in private practice extremely satisfactory. They are capable of further improvement, if one could sufficiently impress upon the people, that it is only by treatment on the first day, that the patient has the best chance of getting over the disease. That time and education are in its favour is shown by the greater use that is now being made of the serum, and the greater confidence of the people in its usefulness and efficacy.





